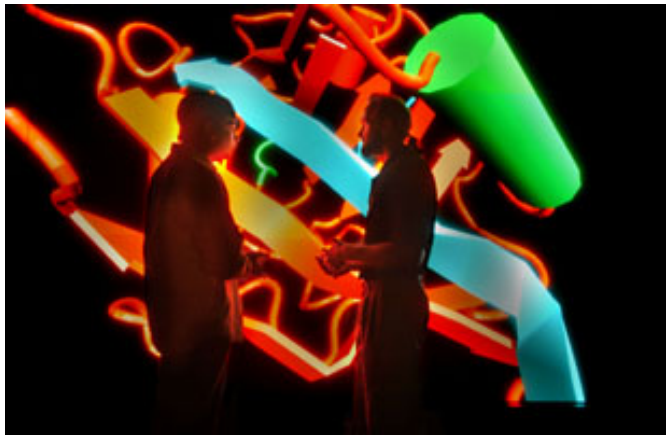
Enabling Next Generation Modeling and Simulations in Biology



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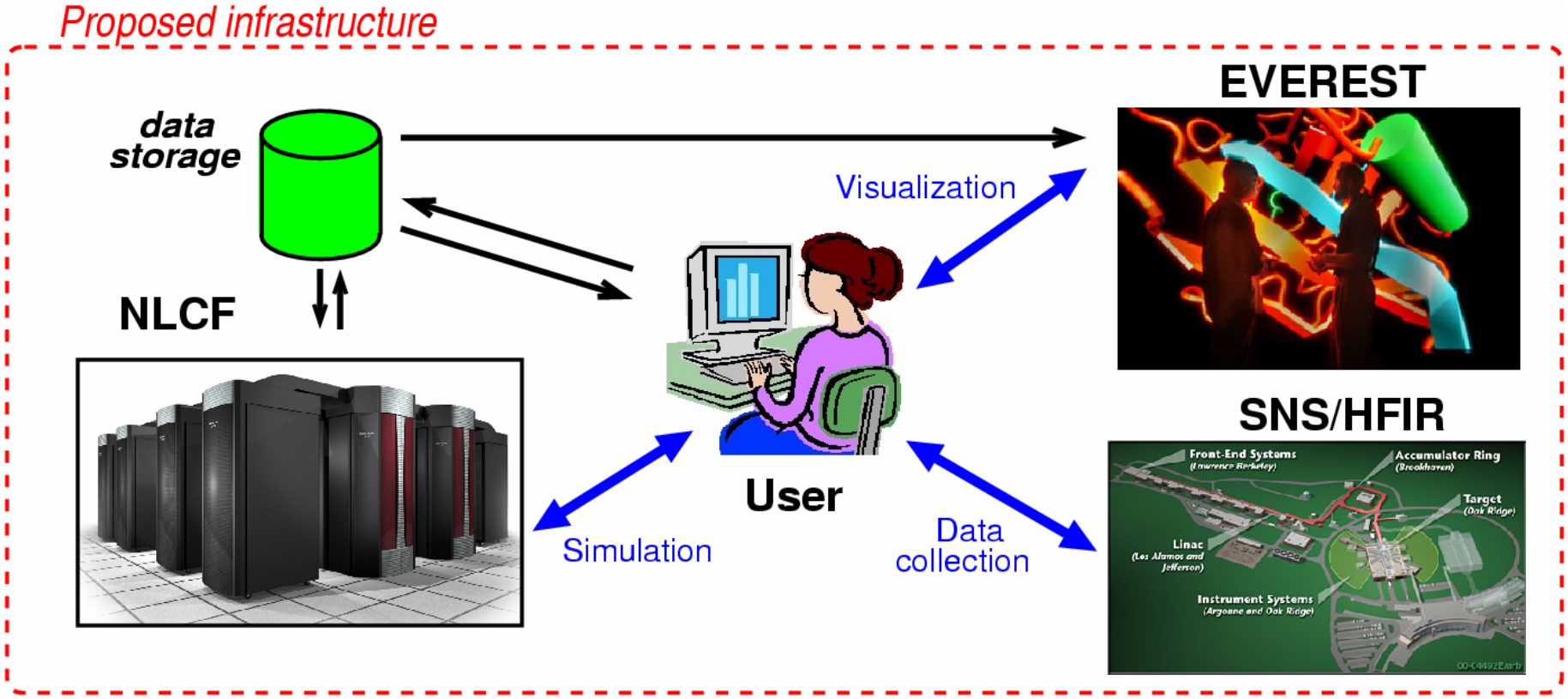
Ed Uberbacher (LSD) and Dean A. A. Myles (CSD)

Oak Ridge National Laboratory

Multi-disciplinary Infrastructure for Next Generation Modeling and Simulations



- Data collection from SNS/HFIR
- Simulations on NLCF machines with teraFLOP power
- Visualization on EVEREST and data storage on HPSS

Significance

- **computational genomics**
- **database design and enhancement**
- ***molecular modeling and simulation***
- **analysis of complex biological systems**
- **cell modeling**
- **biomedical software development**
- **high-throughput data analysis**

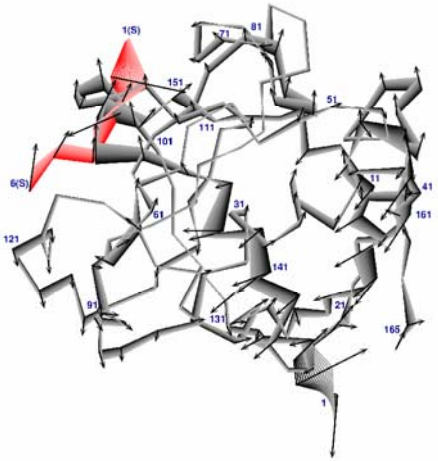
Detailed biophysical characterization of molecular machines, protein structure prediction, docking and others

Multi-scale modeling – Structure, Dynamics and Function

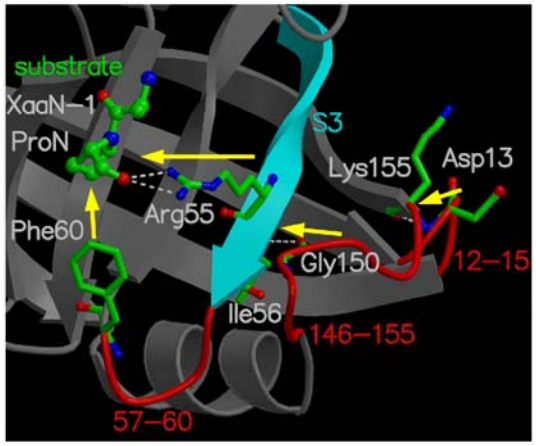
Desired/Current capability Ratio: 10^4-10^6

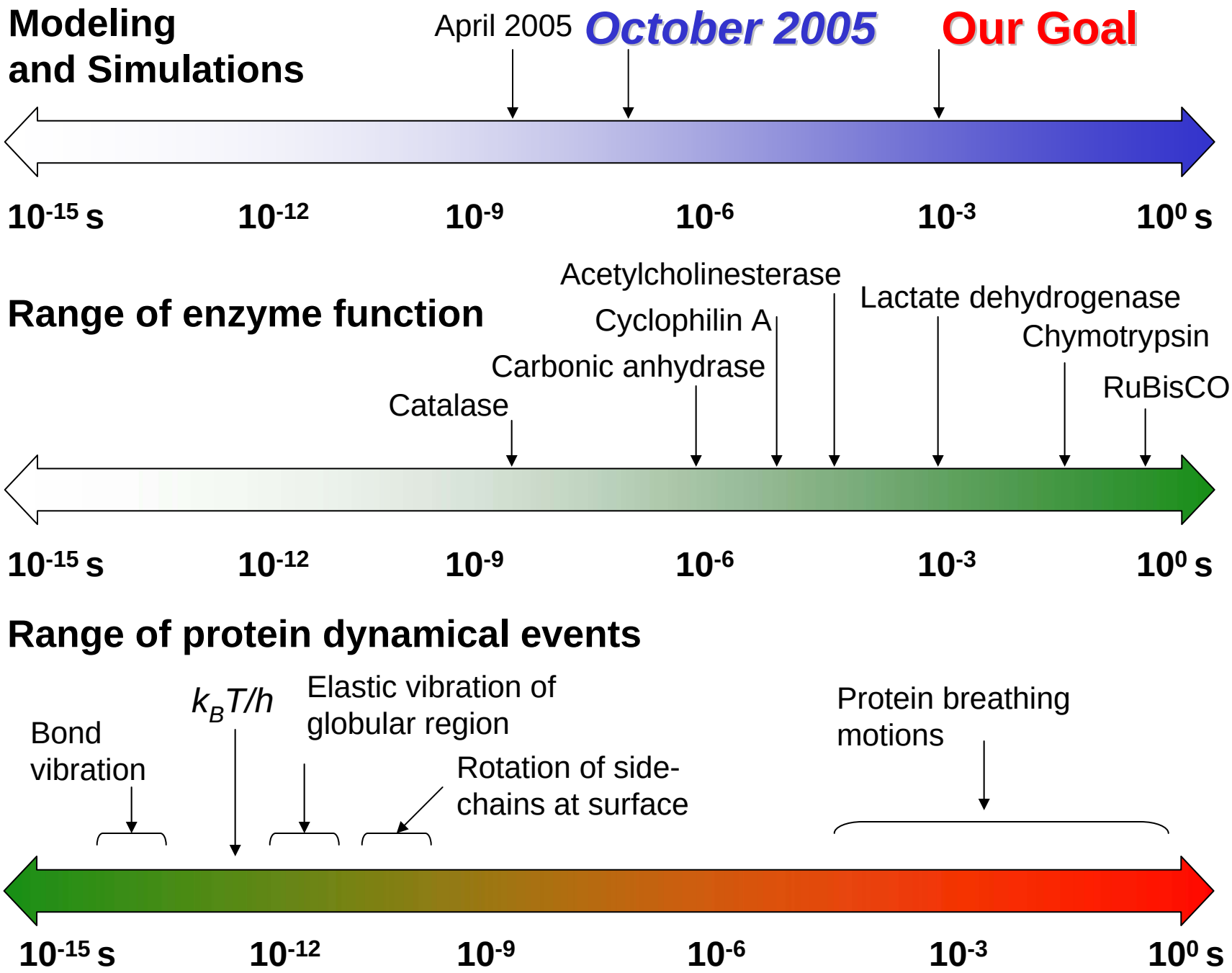
Structure

Dynamics



Function




Modeling
and Simulations
April 2005
October 2005
Our Goal
10-15 s
10-12
10-9
10-6
10-3
100 s
Range of enzyme function
Acetylcholinesterase
Cyclophilin A
Lactate dehydrogenase
Chymotrypsin
Carbonic anhydrase
RuBisCO
Catalase
10-15 s
10-12
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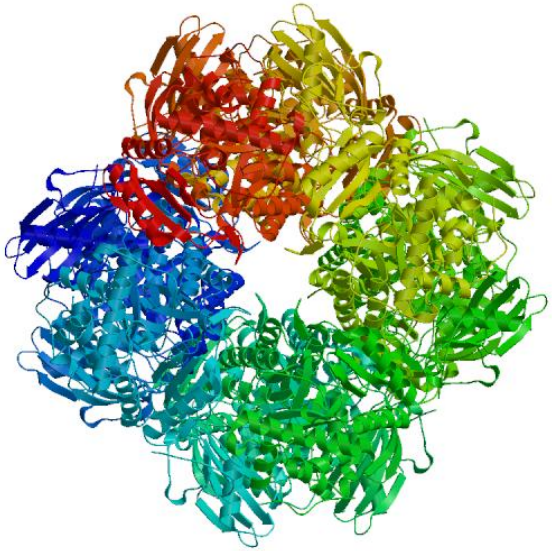
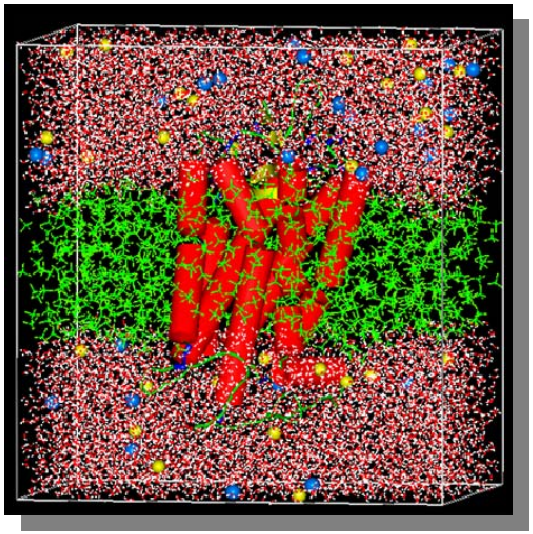
100 s
Range of protein dynamical events
Bond
vibration
kBT/h
Elastic vibration of
globular region
Rotation of side-
chains at surface
Protein breathing
motions
10-15 s
10-12
10-9
10-6
10-3
100 s

Enzyme RuBisCO

- Plays a role in Carbon sequestration
- The enzyme activity is at the order of (10^0) seconds
- Very large enzyme
- Multi-scale modeling needed

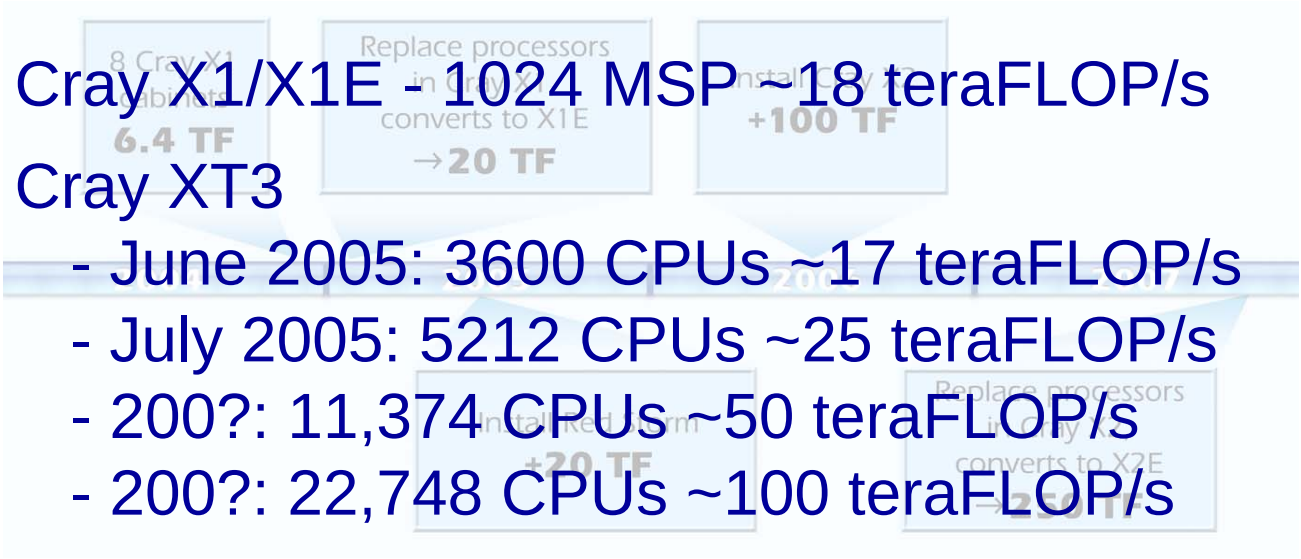


Biological Membranes



- Many cellular functions including transport, signaling and cellular interactions
- Computational modeling and simulations will have broad impact
- In combination with neutron and X-ray scattering, modeling and simulations will provide valuable insights

Porting and optimizing popular MM and QM codes in biology to NLCF machines



- Cray X1/X1E - 1024 MSP ~18 teraFLOP/s
- Cray XT3
  - June 2005: 3600 CPUs ~17 teraFLOP/s
  - July 2005: 5212 CPUs ~25 teraFLOP/s
  - 200?: 11,374 CPUs ~50 teraFLOP/s
  - 200?: 22,748 CPUs ~100 teraFLOP/s

- Popular molecular mechanics (MM) packages
  - AMBER, CHARMM, LAMMPS, NAMD, GROMACS
- Quantum-mechanical (QM) for detailed modeling
  - GAMESS, NWChem
- AMBER: Cheetah Supercomputer
  - speed up ~4 on 8 CPUs & ~8 on 32 CPUs
  - limit of maximum128 processors

Scaling the MD Kernel

$$V(\mathbf{r}^N) = \sum_{bonds} \frac{k_i}{2}(l_i - l_{i,0})^2 + \sum_{angles} \frac{k_i}{2}(\theta_i - \theta_{i,0})^2$$
$$+ \sum_{torsions} \frac{V_n}{2}(1 + cos(n\omega - \gamma))$$
$$+ \sum_{i=1}^{N} \sum_{j=i+1}^{N} \left(4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right)$$

Evaluations of non-bonded interactions most compute intensive part of MD: 80-90% of runtime!

Particle-mesh Ewald (PME) method

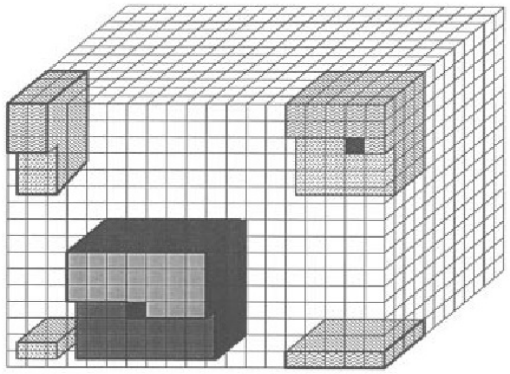
E(electrostatic)

= E(direct)

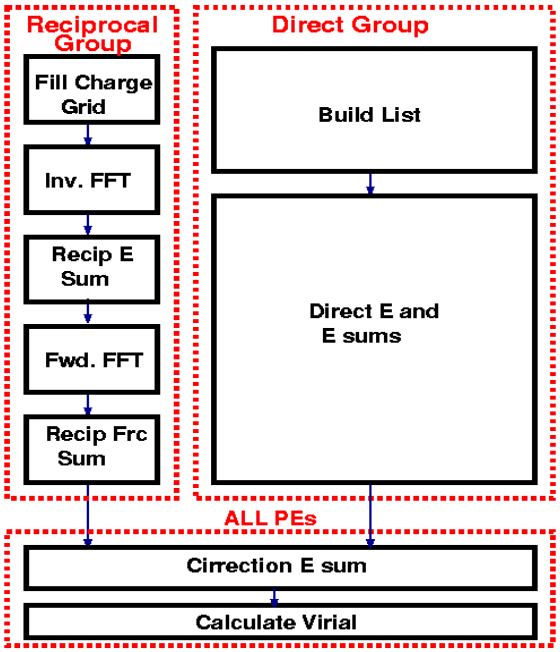
+ E(reciprocal)

+ E(correction)

Non-bonded pair list



Discrete Fourier transform on a grid



Preliminary Performance Analysis

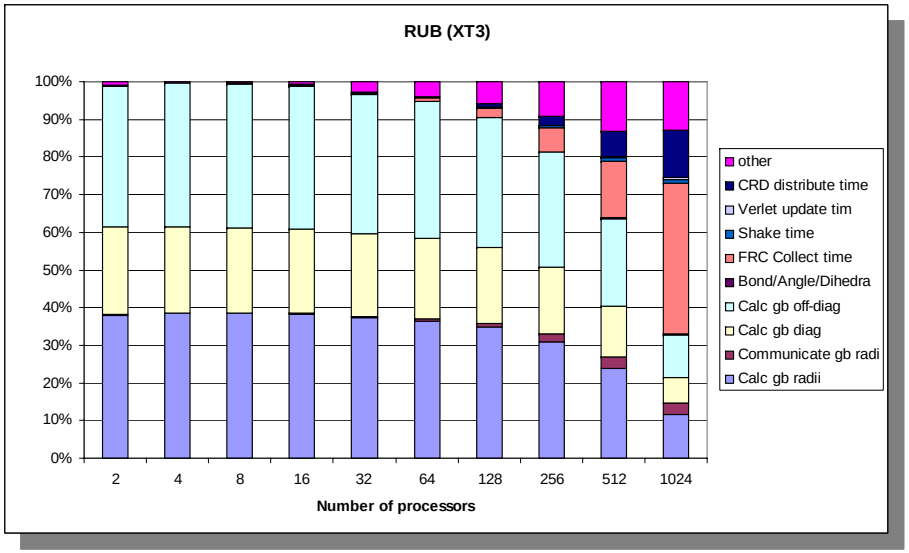
- AMBER scaled beyond 128 processors

  -1024 nodes on IBM BG/L

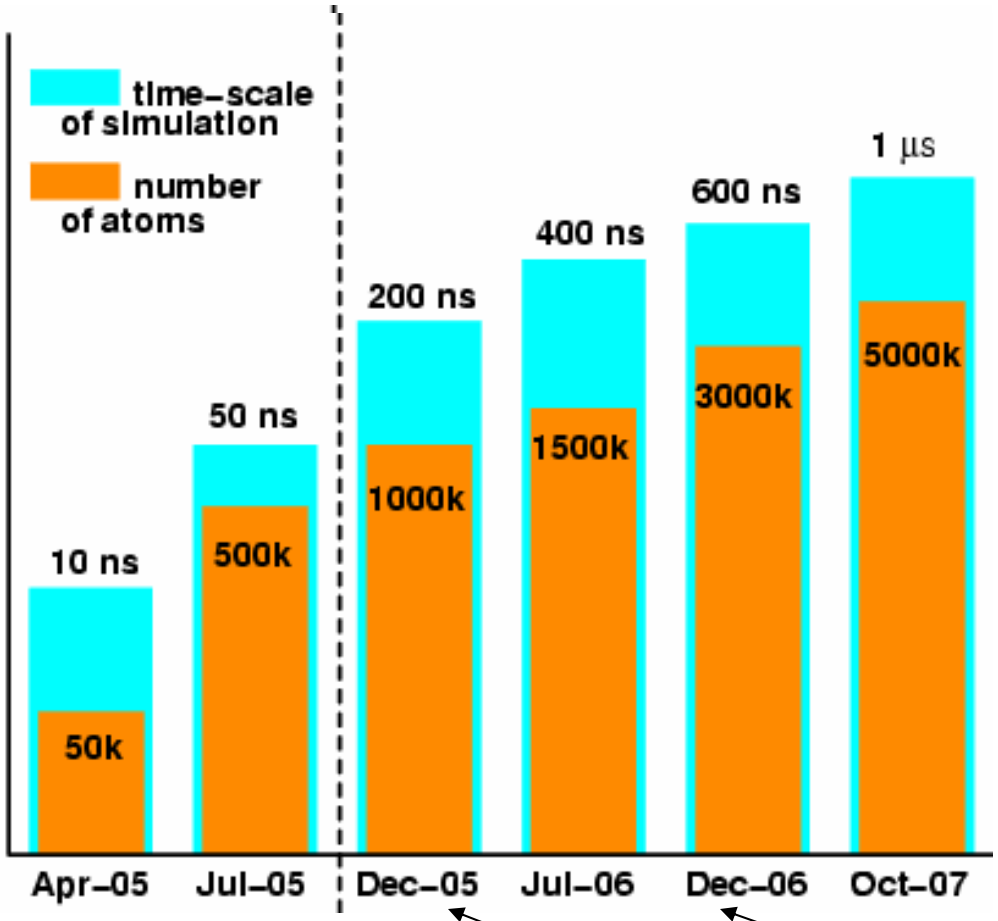
  - 4096 nodes on Cray XT3

- Application profiling: identified code blocks and communication patterns that limit the scalability

- LAMMPS – highly scalable MD engine



Time-line for scaling on NLCF machines



IBM p690
128 processors

ANL BGL
512-vn processors

ORNL XT3
1024 processors

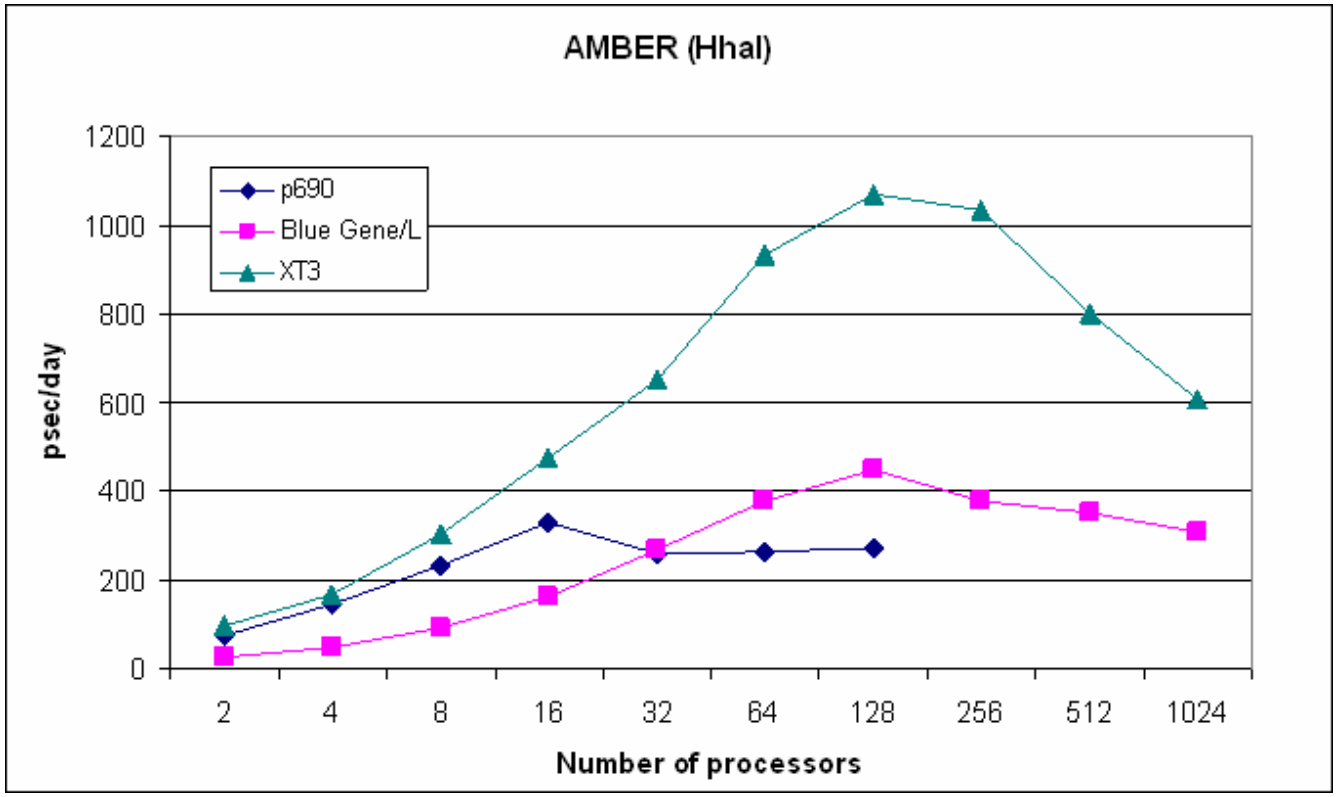
ORNL XT3
4096 processors

ORNL XT3
>16000 processors

200?
100 teraFLOP/s

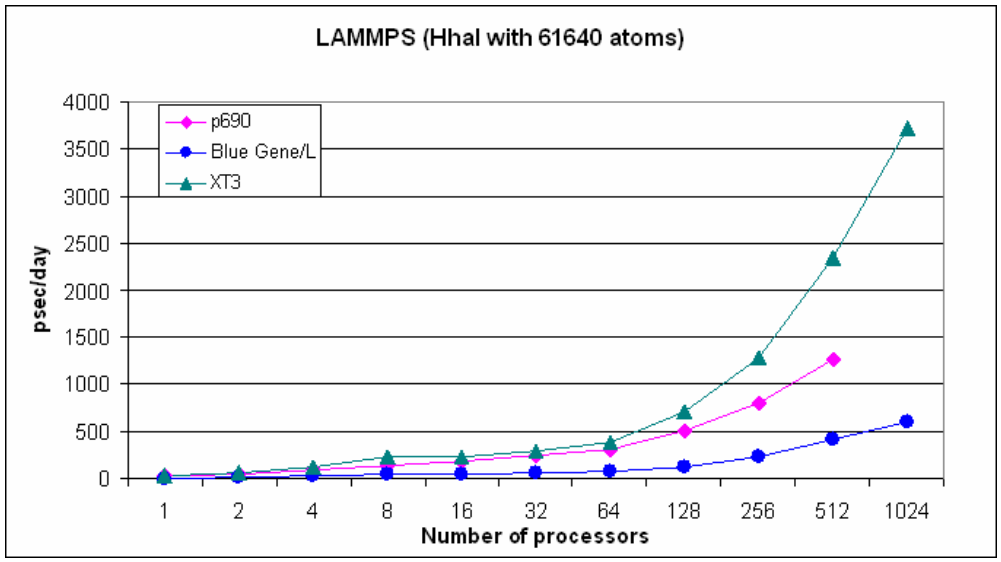
200?
>200 teraFLOP/s

Preliminary work: Scaling studies



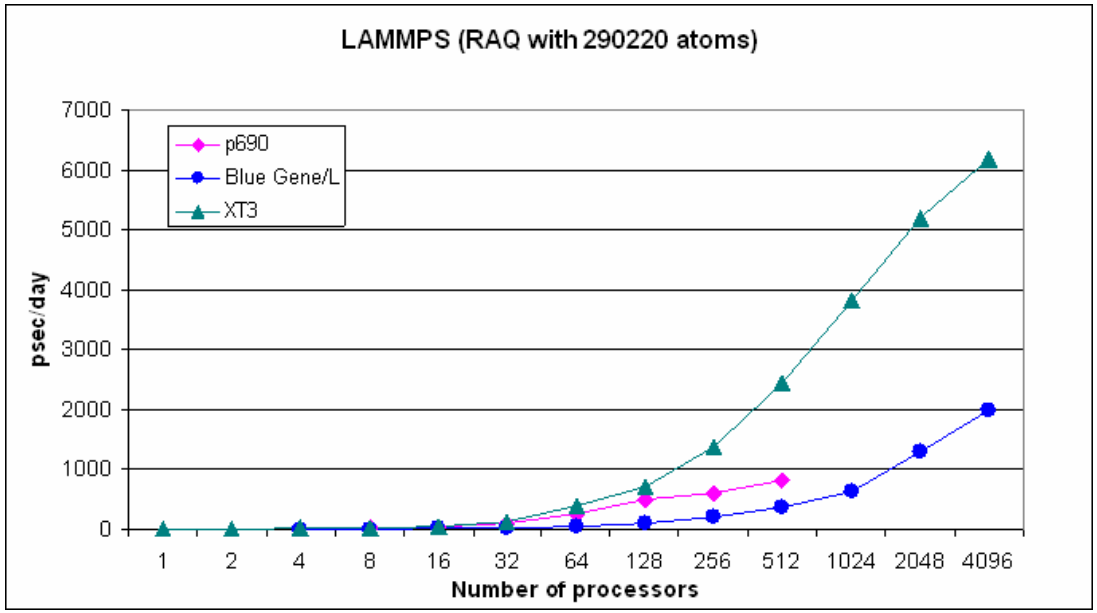
- Molecular dynamics: AMBER (v 8) *sander* module
- Solvated enzyme-DNA complex with about 60,000 atoms

Preliminary work: Scaling studies



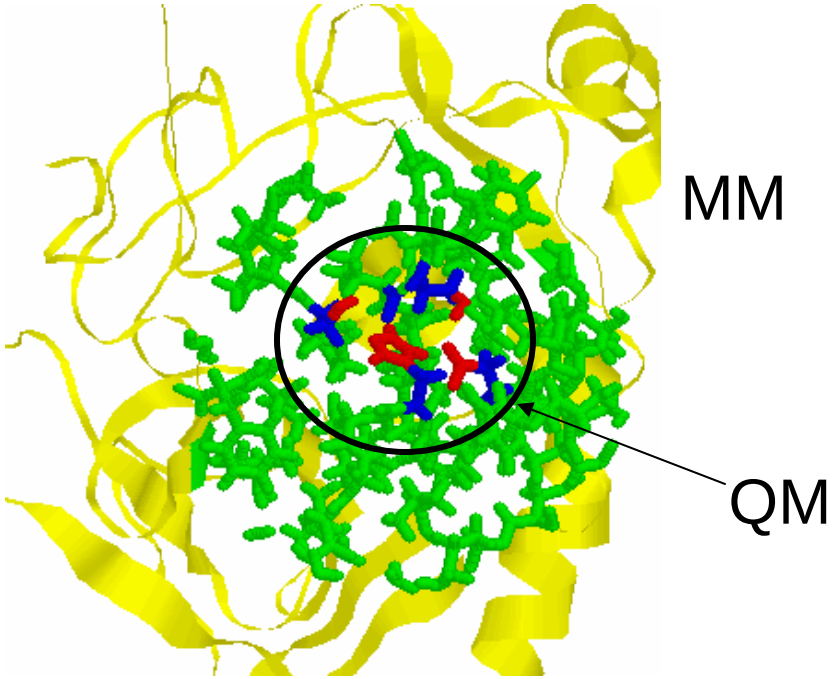
- LAMMPS with AMBER force-field
- Explicit solvent

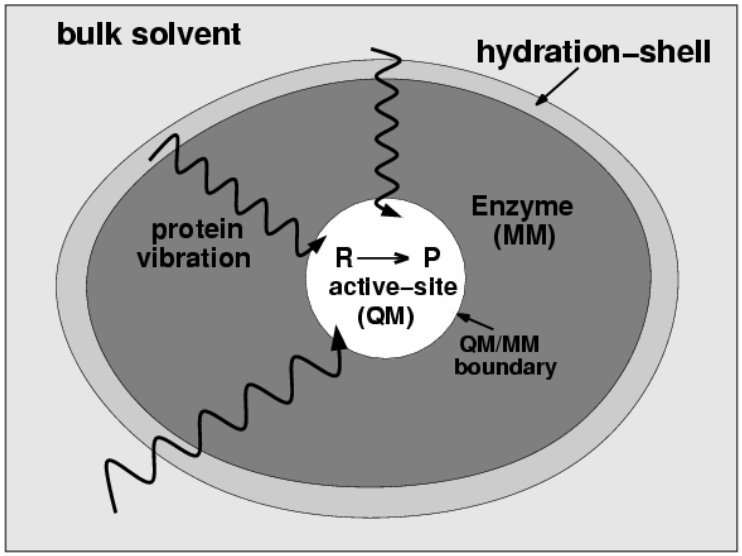
- 30 days - 200 ns!
- ~300K atoms!
- 16,000 processors on IBM Blue Gene/L



Hybrid QM/MM methodology for simulating enzyme catalysis

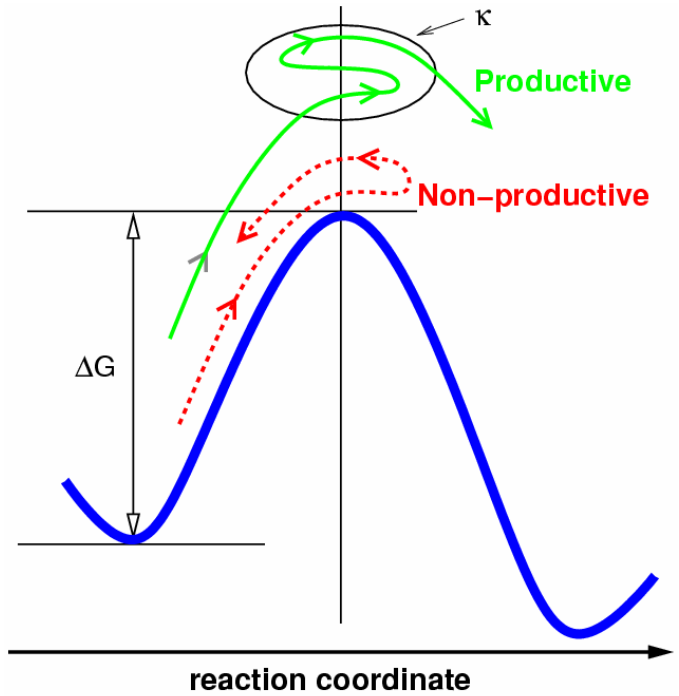
- Accurate treatment of long range electrostatics and dynamics
- Multi-scale protein dynamics: Novel ways to detect reaction coupled vibrational modes
- Explicit solvent: solvent-protein dynamics coupling





Multi-scale modeling

- Enzyme kinetics: Transition state theory
- Multi-scale protein dynamics: GNM, QHA, TANCA
- Fast time-scales (picosecond-microsecond)
- Mechanistic insights: local structure and long range effects
- The effect of dynamical effects on free energy, individual residues (mutants)
- Effect on barrier height and transmission coefficient
- Vibrational mode driven reactions

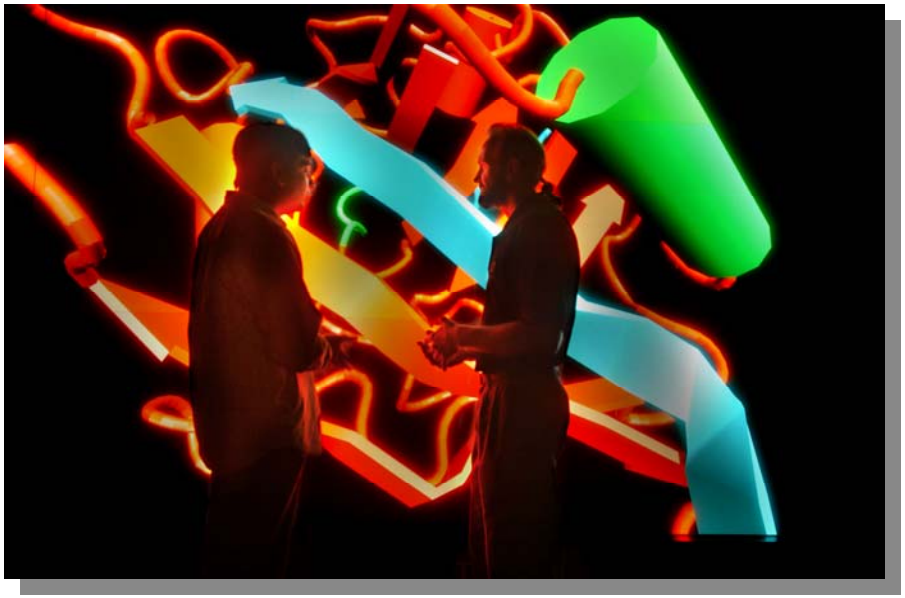


$$k_{TST} = \left(\frac{k_B T}{h}\right) \exp\left(\frac{-\Delta G^{\dagger}}{k_B T}\right)$$

$$k = \kappa k_{TST}$$

Interfacing with visualization facility and data storage

- Visualization of biological data is critical for fast interpretation and analysis of large data sets
- *Network of protein vibrations identified using EVEREST*
- Interface experimental and computational facilities with EVEREST: model low as well as high resolution data

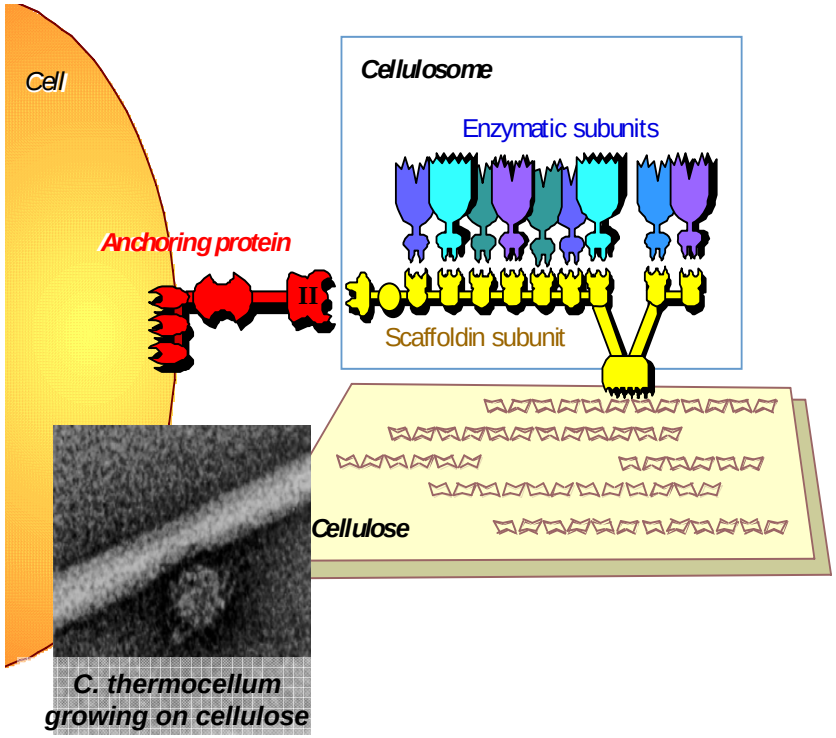


Multi-scale modeling: Cellulose degradation

System of energy research (DOE) interest

- Renewable energy: ethanol production from cellulose
- Detailed understanding of cellulase enzyme mechanisms from multi-scale modeling
  - 1-100 ns trajectories for systems with over 800,000 atoms

- Simulations with different substrates and mutant enzymes
- Creation of more efficient enzymes for cellulose degradation through protein engineering

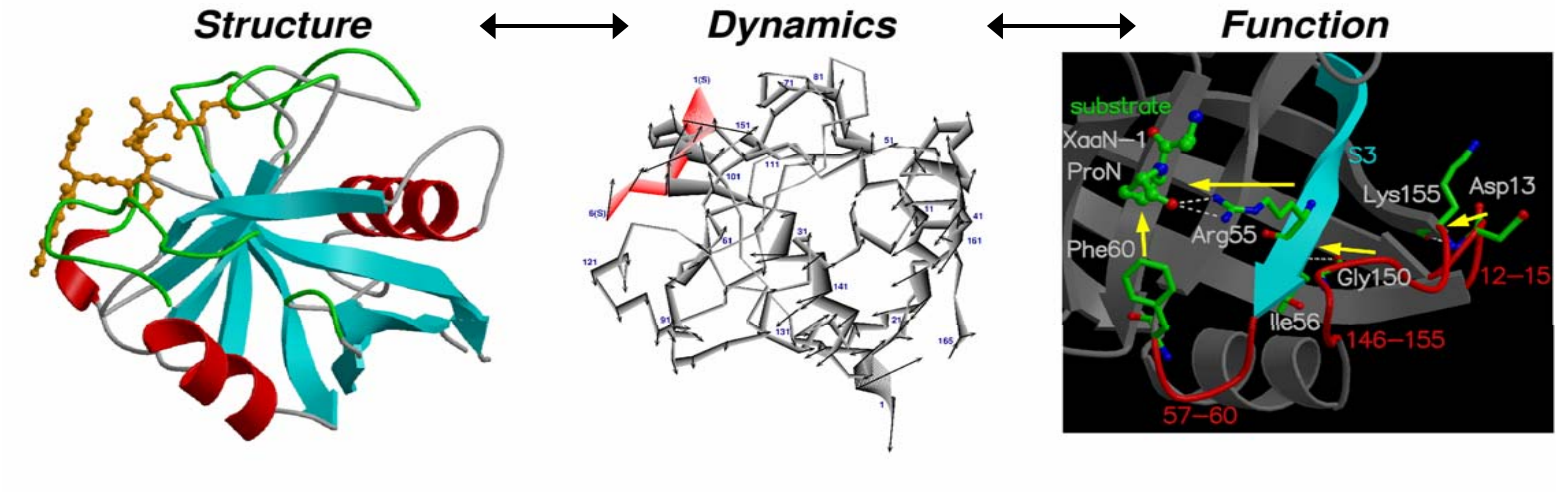


Multi-scale modeling: Enzyme Cyclophilin A

System of medical interest

- Enzyme cyclophilin A plays a role in many cellular function including protein folding and transport
- Required for infectious activity of HIV-1
- Link between enzyme structure, dynamics and function
- Multi-scale modeling lead to identification of

  Network of protein dynamics promoting enzyme catalysis
- Computational finding verified experimentally

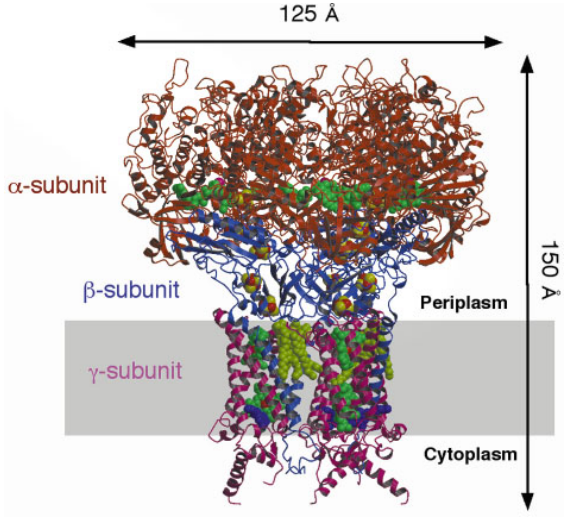


Interfacing simulations with experiments

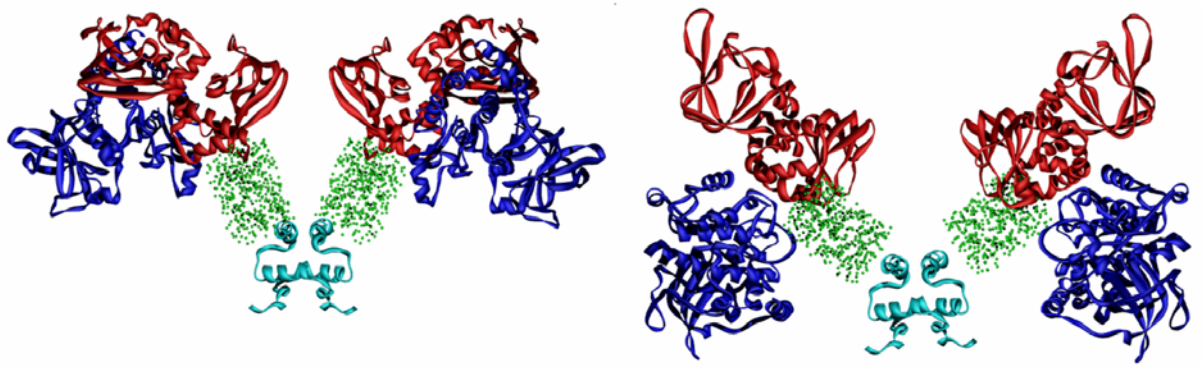
Include data from a variety of experimental techniques into simulations - better models

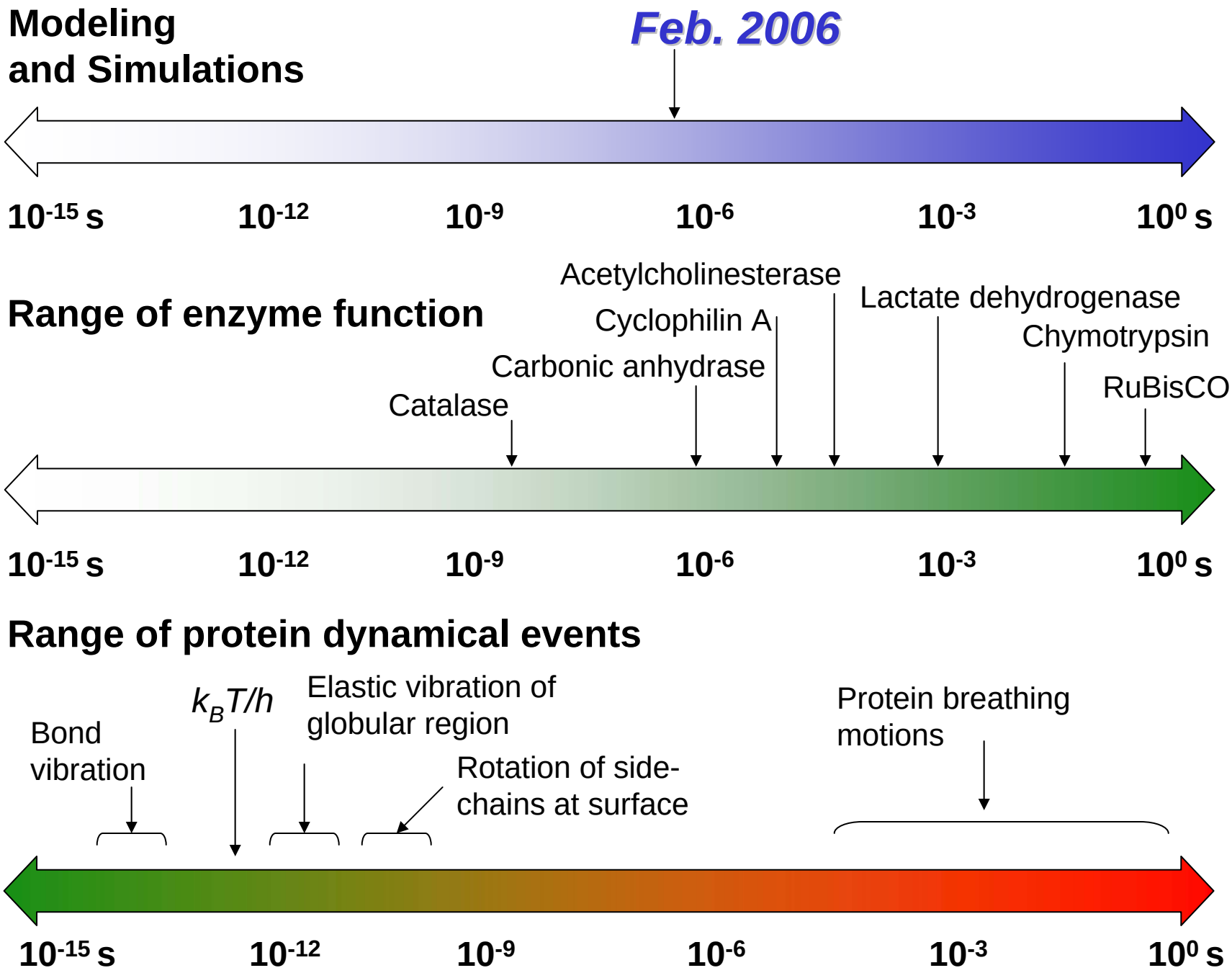
Neutron and X-ray scattering

- RuBisCO
- models of membrane systems
- structure, dynamics and function of biomolecular complexes



Refining low resolution data through modeling & simulations




Modeling
and Simulations
Feb. 2006
10-15 s
10-12
10-9
10-6
10-3
100 s
Range of enzyme function
Acetylcholinesterase
Cyclophilin A
Lactate dehydrogenase
Chymotrypsin
Carbonic anhydrase
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Catalase
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Elastic vibration of
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Protein breathing
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10-15 s
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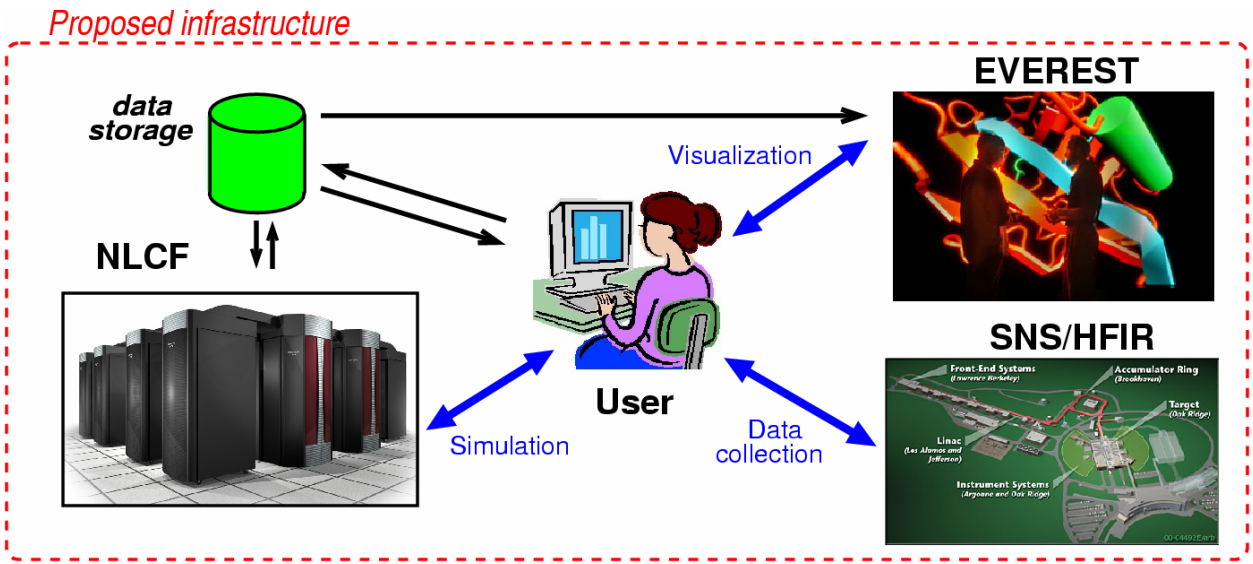
100 s

Summary

- Next Generation Modeling and Simulations
- Integrate ORNL's experimental, computing and visualization facilities
- Biophysical characterization of molecular machines through multi-scale modeling
- Impact Chemistry and Materials/Nanotechnology



Acknowledgements

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- Al Geist
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- NCCS